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THE CIRCULATORY RESPONSE TO SMOKING

CAROLINE BEDELL THOMAS, M.D.
EDMUND A. MURPHY, M.D.
Baltimore, Md.

From the Department of Medicine, The Johns Hopkins University School of Medicine

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THE CIRCULATORY RESPONSE TO SMOKING

The Variation in Ballistocardiographic Smoking Tests in Healthy Young Men

CAROLINE BEDELL THOMAS, M.D.
EDMOND A. MURPHY, M.D.
BALTIMORE, MD.

From the Department of Medicine, The Johns Hopkins University School of Medicine
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DURING the course of a project to discover what characteristics in the individual are of value in recognizing susceptibility to hypertension and coronary heart disease, a study of the circulatory response to smoking in healthy young adults was reported, in 1956, by Thomas, Bateman, and Lindberg.[1] Various patterns of response were described, and the mean patterns of subjects grouped on the basis of sex, body weight, smoking habits, or family history were compared. The most striking differences found were those associated with family history. On the average, subjects with a history of parental hypertension appeared much more reactive than did those with normal parents, while subjects with a history of parental coronary disease showed less response of blood pressure, heart rate, and cardiac output than either of the other two groups. Since both hypertension and coronary disease are thought to depend in part on genetic factors, these varying patterns of circulatory response to smoking may stem from inherited constitutional differences. If so, they would provide early indications of liability to cardiovascular disease in later life.

It is clear that differences in the pattern of response to smoking arise from two main sources of variation—true "constitutional" differences between individuals, and variations in physiologic responsiveness of the individual from time to time. It is also clear that however valuable this test may be in distinguishing between different groups, it will be of little value in individual prognosis unless the former source of variation is much more important than the latter. Accordingly, studies have been undertaken (1) to measure the reproducibility of results under standard conditions, and (2) to ascertain what factors influence the results and therefore should be standardized if the maximum amount of information is to be derived from smoking tests.

This study was supported in part by the Tobacco Industry Research Committee, in part by Research Grant H-1891, National Heart Institute and in part by Research Contract V1001 M-2768, Veterans Administration.

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MATERIALS AND METHODS OF PROCEDURE

All the subjects were Johns Hopkins medical students in good health and free from clinical, electrocardiographic, and ballistocardiographic evidences of hypertension or coronary heart disease. They were of comparable age and were all male smokers. The same Technitrol table ballistocardiograph was used throughout. The details of the method used in performing the smoking test and in analyzing the ballistocardiographic measurements were as previously described.[1]

Three series of smoking tests provided material for this study.

Series O.—Number of subjects: 69. Mean age in years at last birthday: 24.86 ±0.27.

Of the 113 individuals whose single smoking tests have already been reported, 69 were male smokers.[1] The data for these subjects are here freshly analyzed after excluding the female subjects and the nonsmokers for the sake of homogeneity. These tests were performed at various times of day from 9:30 A.M. to 5:20 P.M. Two-thirds were performed between 2:30 P.M. and 5:00 P.M. With rare exceptions, at least 1 hour had elapsed since the last meal.

Series F.—Number of subjects: 32. Mean age in years at last birthday: (1) for "I" tests 23.16 ±0.27, (2) for "II" tests 23.31 ±0.26.

Four smoking tests were performed on each of the 32 male smokers in the class of 1958, between October, 1955, and June, 1956. The four tests on each individual consisted of two tests on each of two days (I and II), one before breakfast (A) and one before lunch (B). The first pair of tests (IA and IB) was carried out on a day in the fall of 1955, the second pair (IIA and IIB) on a day during that winter or in the spring of 1956. All of the 128 tests were performed by one of three assistants; almost always, each pair of tests was carried out by the same assistant.* The subject came to the laboratory at 8:00 A.M. without smoking, without breakfast, and without drinking coffee. He was weighed and measured, after which he lay quietly on the ballistocardiograph. The A test was then done in accordance with the method previously described except that the subject smoked one cigarette instead of two, and no electrocardiographic tracings were recorded.[1] After the A test he breakfasted, smoked if he pleased, and attended morning classes as usual, returning to the laboratory before lunch for the second (B) test of the day. He was not, however, allowed to smoke between 12:00 noon and his B test which was performed at 1:00 P.M.

The two tests on the same day, then, differed in the following respects: (1) for the A test the subject had been fasting overnight, for the B test for the 4 hours since breakfast only; (2) the subject was allowed to smoke up to 1 hour before his B test, but not for 8 hours before his A test; and (3) he had been inactive for most of the previous 8 hours before the A test, whereas before his B test, he had been occupied with the usual second year academic activities.

*We should like to acknowledge the assistance of Dr. Amarili Kassam, part-time fellow, who performed many of the smoking tests.

The tests on the second day (IIA and IIB) were carried out as nearly as possible in the same manner as those on the first day.

Series E.—Number of subjects: 6. Mean age in years at last birthday: (1) at first test 23.33 ±0.42, (2) at last test 23.67 ±0.33.

Over a period of 9 weeks in the summer of 1956, each of 6 male smokers underwent a series of eight smoking tests performed as far as possible under circumstances identical for each individual and conducted by the same observer (EAM). On the 8 test days, each subject followed a uniform pattern of activity, took a uniform amount of exercise, smoked the same number of cigarettes at the same time of day, and ate the same types of meals at the same times of day. The tests were performed at a time of day constant within 5 minutes either way for each individual, and all between 2:00 and 5:00 P.M. (resembling the majority of studies in series O). Since the period of time over which the observations were made was brief, weather conditions were fairly constant. It will thus be seen that while there were differences *between* individuals, for any *one* individual, the circumstances were as nearly as possible absolutely uniform. The ballisto-cardiographic measurements were all made by the same two technical assistants working together.

Consideration of these three series shows a varying degree of standardization: (1) series O: in this series all subjects were healthy young male smokers; (2) series F: all the subjects were healthy young male smokers and the tests were performed at two standard times of day under two standard conditions of smoking and eating; (3) series E: all the subjects were healthy young male smokers, whose eating, smoking, and exercise habits were, within the individual, uniform and the observer and the time at which the test was performed unvaried. The weather conditions were also fairly constant.

Most of the statistical techniques used in these analyses are described in Snedecor's textbook.[2] The use of "t" tests has been restricted to groups of figures found to have a normal distribution. The meaning of asterisks to denote levels of significance is defined in the footnotes.

RESULTS

The Interindividual Range of Circulatory Response to Smoking: the Series of Single Smoking Tests in 69 Subjects (Series O).—The means and variances for the results obtained in the 69 single smoking tests (Series O) are shown in Table I. Despite the greater homogeneity of the present group as the result of discarding the nonsmokers and the women, the findings are essentially the same as those for the 113 individuals set forth in the first table of the preceding paper.[1] The main importance of the new calculations here given in Table I is for the purposes of comparison with groups E and F (see below).

Comparison of Variation Within the Individual and Between Individuals Under Different Standardized Fasting Conditions: the Series of Two Tests Before Breakfast and Before Lunch on Each of 32 Subjects (Series F).—The results of

TABLE I. ANALYS

MEASUREMENT
Systolic pressure
Control
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Pulse pressure
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Heart rate
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TABLE I. ANALYSIS OF RESULTS OBTAINED IN 69 SINGLE SMOKING TESTS ON MALE SMOKERS

MEASUREMENT	MEAN	(S.D.)[2]	S.D.	S.E.M.
Systolic pressure				
Control	114.2	92.66	9.63	1.16
Change	2.61***	36.48	6.04	0.73
Final	116.8	100.84	10.04	1.21
Diastolic pressure				
Control	71.6	49.44	7.03	0.85
Change	4.93***	24.19	4.92	0.59
Final	76.6	59.28	7.70	0.93
Pulse pressure				
Control	42.6	87.37	9.35	1.13
Change	−2.32**	45.04	6.71	0.81
Final	40.2	102.72	10.14	1.22
Heart rate				
Control	70.8	122.03	11.05	1.33
Change	7.50***	48.01	6.93	0.83
Final	78.3	131.18	11.45	1.38
Stroke volume				
Control	109.7	250.07	15.81	1.90
Change	−3.84***	43.91	6.63	0.80
Final	105.9	297.48	17.25	2.08
Cardiac output				
Control	7.69	1.585	1.259	0.152
Change	0.473***	0.559	0.748	0.090
Final	8.16	2.081	1.443	0.174

These probability values are based on "t" tests for significance of change on smoking as compared with the variation in the change on smoking.

Probabilities are indicated by asterisks as follows:

* P < 0.05
** P < 0.01
***P < 0.001

Abbreviations: S.D. = standard deviation; S.E.M. = standard error of the mean.

Blood pressure is recorded throughout in mm. Hg, heart rate in beats per minute, stroke volume in milliliters, and cardiac output in liters per minute.

this series of 128 smoking tests on 32 subjects are summarized in Table II.* Smoking one cigarette produces, in each instance, a highly significant mean rise in systolic and diastolic pressure, heart rate, and cardiac output and a significant mean fall in stroke volume. In the main, the systolic and diastolic pressures rise in parallel so that the mean pulse pressure is little affected. In Test IIB, however, the pulse pressure falls by an amount which is just significant. This pattern is substantially the same as that in the O series; the higher probability of significance for the change in the pulse pressure in the latter is in part a reflection of the larger number of observations.

*Because one of the series of ballistocardiograms was technically unsatisfactory in each of two subjects, all the calculations derived therefrom (heart rate, stroke volume, and cardiac output) were discarded. Thus there are data on blood pressure in 32 subjects and on the cardiac measurements in 30.

TABLE II. THE EFFECTS OF SMOKING UNDER DIFFERENT CONDITIONS IN THE FASTING STATE: FOUR TESTS ON EACH OF 32 MALE SMOKERS (SERIES F)

OBSERVATION	N	IA. THE FIRST TEST BEFORE BREAKFAST					IIA. THE SECOND TEST BEFORE BREAKFAST				
		CONTROL MEAN	CHANGE AFTER ONE CIGARETTE				CONTROL MEAN	CHANGE AFTER ONE CIGARETTE			
			MEAN	S.D.	S.E.M.	t		MEAN	S.D.	S.E.M.	t
Systolic pressure	32	113.2	+5.4	6.56	1.16	4.63***	112.9	+6.5	6.49	1.15	5.70***
Diastolic pressure	32	66.3	+5.1	5.49	0.97	5.21***	67.0	+6.0	5.63	1.00	5.90***
Pulse pressure	32	46.9	+0.3	4.54	0.80	0.39	45.9	+0.7	4.27	0.75	0.87
Heart rate	30	60.8	+13.3	10.3	1.88	7.09***	60.0	+13.3	12.1	2.20	6.06***
Stroke volume	30	109.4	−6.2	10.1	1.84	3.35**	110.6	−5.5	9.46	1.73	3.18**
Cardiac output	30	6.57	+1.03	0.99	0.18	5.72***	6.60	+1.10	1.26	0.23	4.76***
		IB. THE FIRST TEST BEFORE LUNCH					IIB. THE SECOND TEST BEFORE LUNCH				
Systolic pressure	32	115.0	+2.4	3.22	0.57	4.28***	115.5	+4.3	5.23	0.93	4.70***
Diastolic pressure	32	67.0	+3.5	4.20	0.74	4.67***	66.9	+6.0	5.05	0.89	6.69***
Pulse pressure	32	48.0	−1.0	3.83	0.68	1.52	48.6	−1.6	4.50	0.80	2.04*
Heart rate	30	63.1	+11.7	8.56	1.56	7.47***	64.0	+9.3	6.29	1.15	8.12***
Stroke volume	30	111.0	−6.5	9.13	1.67	3.92***	115.2	−7.0	7.75	1.41	4.97***
Cardiac output	30	6.96	+0.78	0.89	0.16	4.82***	7.31	+0.55	0.81	0.15	3.60***

Tests IA, IB, IIA and IIB are further described in the text; this system of numbering is used throughout the tables for Series F.
*P < 0.05
**P < 0.01
***P < 0.001
Abbreviations: S.D. = standard deviation; S.E.M. = standard error of the mean.

From further examination of Series F, it is possible to study the effect of several factors on the circulatory response to smoking.

The influence of time of day: The effect of time of day on the control readings may be seen in the upper part of Table III where the means of the paired differences are compared with their variances to give t values as tests of significance. On the first day (IA-IB), although all the differences are negative, i.e., the control values are higher before lunch than before breakfast, none of these differences is statistically significant. On the second day (IIA-IIB), however, all the prelunch readings are significantly higher than the prebreakfast readings excepting the diastolic pressure which is virtually the same in the two groups.

Similar statistical comparisons made of the change produced by smoking one cigarette, are set forth in the lower half of Table III. These results are complementary to those above. On the first day (IA-IB) there is a greater response to smoking before breakfast, although in only one measurement—the systolic pressure—is the change significant at the 5 per cent level. On the second day (IIA-IIB) systolic and pulse pressure, heart rate, and cardiac output show a bigger rise before breakfast. These findings tally with the subjective observation by many smokers that the first cigarette in the morning has more effect than any other, especially if it is smoked in the fasting state.

TABLE III. MEAN DIFFERENCES IN CONTROL VALUES AND IN CHANGES ON SMOKING (SERIES F)

MEASUREMENT	IA–IB		IIA–IIB		IA–IIA		IB–IIB	
	MEAN DIFFERENCE	t	MEAN DIFFERENCE	t	MEAN DIFFERENCE	t	MEAN DIFFERENCE	t
Control value								
Systolic pressure	−1.78	1.96	−2.59	2.91**	+0.31	0.21	−0.50	0.39
Diastolic pressure	−0.66	0.61	+0.03	0.05	−0.66	0.39	+0.03	0.02
Pulse pressure	−1.12	1.04	−2.62	2.92**	+0.97	0.58	−0.53	0.34
Heart rate	−2.23	1.97	−4.00	3.24**	+0.80	0.68	−0.97	0.69
Stroke volume	−1.57	0.72	−4.57	2.74*	−1.23	0.42	−4.23	2.11*
Cardiac output	−0.38	2.03	−0.71	4.39***	−0.03	0.14	−0.36	1.77
Change after smoking								
Systolic pressure	+2.94	2.48*	+2.19	2.52*	−1.16	0.88	−1.91	2.36*
Diastolic pressure	+1.59	1.40	−0.09	0.12	−0.81	0.67	−2.50	2.87**
Pulse pressure	+1.34	1.16	+2.28	2.36*	−0.34	0.29	+0.59	0.63
Heart rate	+1.67	1.17	+3.97	2.52*	+0.03	0.02	+2.33	1.66
Stroke volume	+0.37	0.16	+1.53	0.68	−0.67	0.27	+0.50	0.27
Cardiac output	+0.25	1.62	+0.54	3.14**	−0.07	0.35	+0.23	1.50

* P < 0.05
** P < 0.01
*** P < 0.001

We have commented above that the "control" and "change" figures are complementary, and, in fact, the "final" figures (or absolute readings after smoking) are quite remarkably constant (Table IV and Fig. 1). When "t" tests on the paired differences are examined on the null hypothesis, the only difference from zero which is significant is the stroke volume on the second day (Table V).

Tests IA, IB, IIA and IIB are further described in the text; this system of numbering is used throughout the tables for Series F.
*P < 0.05
**P < 0.01
***P < 0.001
Abbreviations: S.D. = standard deviation; S.E.M. = standard error of the mean.

TABLE IV. COMPARISON OF MEANS OF CONTROL VALUES, CHANGES AND FINAL VALUES IN SERIES F SMOKING TESTS

MEASUREMENT	BEFORE BREAKFAST		BEFORE LUNCH	
	FIRST DAY	SECOND DAY	FIRST DAY	SECOND DAY
	IA	IIA	IB	IIB
Systolic pressure				
Control	113.2	112.9	115.0	115.5
Change	+ 5.4	+ 6.5	+ 2.4	+ 4.3
Final	118.6	119.4	117.4	119.8
Diastolic pressure				
Control	66.3	67.0	67.0	66.9
Change	+ 5.1	+ 5.9	+ 3.5	+ 6.0
Final	71.4	72.8	70.4	72.9
Pulse pressure				
Control	46.9	45.9	48.0	48.6
Change	+ 0.3	+ 0.7	− 1.0	− 1.6
Final	47.2	46.6	47.0	46.9
Heart rate				
Control	60.8	60.0	63.1	64.0
Change	+13.3	+13.3	+11.7	+ 9.3
Final	74.2	73.3	74.7	73.4
Stroke volume				
Control	109.4	110.6	111.0	115.2
Change	− 6.2	− 5.5	− 6.5	− 7.0
Final	103.2	105.1	104.4	108.2
Cardiac output				
Control	6.57	6.60	6.96	7.31
Change	+ 1.03	+ 1.10	+ 0.78	+ 0.55
Final	7.60	7.70	7.74	7.86

The adaptation factor: Since the IA test was the first smoking test performed on each of these subjects, it might be thought that on that occasion the subjects would be somewhat tense or apprehensive and that they would be more relaxed during subsequent tests. We have called the effects of familiarity with the test the "adaptation factor." This factor will be studied more closely and over a longer period in the analysis of Series E. In Series F, however, we can note what differences, if any, exist between the first and the second day. In the control values (Table III, IA-IIA, and IB-IIB) only the prelunch stroke volume is significantly different at the 5 per cent level. Comparison of the effect of smoking shows that the rises in systolic and diastolic pressures are significantly greater on the second day before lunch (Table III). None of the other differences is significant. Comparing the final figures shows no significant differences, although the trends are absolutely uniform: pulse pressures and heart rates are higher on the first than on the second day, while the other measurements are lower (Table V). It appears then that adaptation is an unimportant factor in the smoking test, a view which is confirmed in Series E.

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BEFORE LUNCH	
ST DAY	SECOND DAY
IB	IIB
15.0	115.5
2.4	+ 4.3
7.4	119.8
7.0	66.9
3.5	+ 6.0
0.4	72.9
8.0	48.6
1.0	− 1.6
7.0	46.9
3.1	64.0
1.7	+ 9.3
4.7	73.4
1.0	115.2
5.5	− 7.0
4.4	108.2
.96	7.31
.78	+ 0.55
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Effects of smoking habits: An attempt has been made to see whether or not smoking habits influence either the control levels or the response to smoking. Statistically, this factor would be best studied as a regression. Not all the subjects were cigarette smokers, however, and it is difficult if not impossible to express an exact equivalent in cigarettes for the number of cigars or the amount of pipe tobacco smoked. It was, therefore, decided to divide the subjects into "lighter" and "heavier" smokers, the dividing line for cigarettes being 10 per day. By a fortunate chance the cigar and pipe smokers readily fell into this

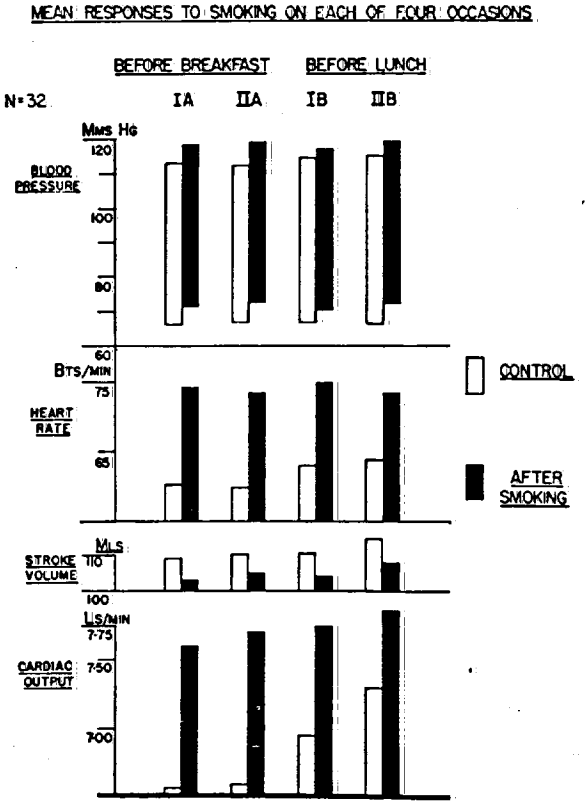

Fig. 1.—The relative constancy of the final postsmoking values under different circumstances. In order to represent small differences, only the upper portions of the columns for heart rate, stroke volume, and cardiac output are shown. For this reason, changes on smoking appear exaggerated.

classification, being all obviously very heavy or very light smokers. The division of subjects gave 12 lighter and 20 heavier smokers; as these numbers are small and any differences are also small, the results of all four tests were pooled for each smoking habit group, giving for the lighter smokers 48 complete sets of results and for the heavy smokers 80 sets of blood pressure readings and 72 sets of cardiac measurements (since both subjects with incomplete ballistocardiographic data were heavy smokers). The numbers of degrees of freedom in the comparisons between these two groups are to all intents and purposes infinitely large. Nothing was lost by pooling, since it transpired that the mean variance

TABLE V. PAIRED DIFFERENCES BETWEEN FINAL VALUES IN FOUR SMOKING TESTS (SERIES F)

FINAL MEASUREMENTS	IA–IB		IIA–IIB		IA–IIA		IB–IIB		IA–IIB		IIA–IB	
	MEAN DIFFERENCE	t	MEAN DIFFERENCE	t	MEAN DIFFERENCE	t	MEAN DIFFERENCE	t	MEAN DIFFERENCE	t	MEAN DIFFERENCE	t
Systolic pressure	+1.16	0.87	−0.41	0.43	−0.84	0.48	−2.41	1.88	−1.25	0.68	+2.00	1.55
Diastolic pressure	+0.94	1.27	−0.06	0.07	−1.47	0.71	−2.47	1.41	−1.53	0.83	+2.41	1.24
Pulse pressure	+0.22	0.17	−0.34	0.34	+0.62	0.39	+0.06	0.04	+0.28	0.16	−0.41	0.27
Heart rate	−0.57	0.46	−0.03	0.02	+0.83	0.67	+1.37	0.88	+0.80	0.65	−1.40	0.71
Stroke volume	−1.20	0.79	−3.03	2.29*	−1.90	1.12	−3.73	1.92	−4.93	2.36*	+0.70	0.41
Cardiac output	−0.13	0.87	−0.17	0.95	−0.09	0.05	−0.13	0.71	−0.26	1.41	−0.04	0.17

*P < 0.05.

in the pooled group in each instance was very little more than that for the individual group of tests. It is clear, then, that the standard error was little more than half as great (since the number of observations is four times as great and the standard error varies inversely as the square root of the number of observations). The results obtained, set forth in Table VI, do not show much difference between the two groups. Lighter smokers have almost always higher control values and show less change on smoking. The results in the final figures are

TABLE VI. THE EFFECTS OF SMOKING HABITS ON THE RESULTS OF THE SMOKING TESTS (SERIES F)

MEASUREMENT	LIGHT SMOKERS (L) MEAN	HEAVY SMOKERS (H) MEAN	L–H	t
Systolic pressure				
Control	116.65	112.66	+ 3.99	2.910**
Change	+ 3.44	+ 5.41	− 1.97	1.910
Final	120.08	118.08	+ 2.01	1.079
Diastolic pressure				
Control	67.79	66.20	+ 1.59	1.144
Change	+ 4.96	5.18	− 0.22	0.227
Final	72.75	71.38	+ 1.37	0.723
Pulse pressure				
Control	48.85	46.46	+ 2.39	1.737
Change	− 1.52	+ 0.24	− 1.76	2.350*
Final	47.33	46.70	+ 0.63	0.418
Heart rate				
Control	63.92	60.71	+ 3.21	2.088*
Change	+ 9.98	+13.19	− 3.21	1.720
Final	73.90	73.90	0.00	0.000
Stroke volume				
Control	110.33	112.36	− 2.03	0.689
Change	− 5.81	− 6.64	+ 0.83	0.493
Final	104.52	105.72	− 1.20	0.451
Cardiac output				
Control	7.03	6.75	+ 0.28	1.315
Change	+ 0.65	+ 1.01	− 0.36	1.863
Final	7.68	7.76	− 0.08	0.323

Where in the above comparisons variance is significantly different in the two groups, probability values are calculated from weighted t values (Cochran's technique).

* $P < 0.05$.
** $P < 0.01$.

much more evenly distributed and none of the differences reaches the significant level. There are no grounds for pairing the individual subjects, but if we compare the mean values for lighter and heavier smokers in tests IA, IB, IIA, and IIB separately, we can study consistency of trends. The results so obtained are laid out in Table VII. This shows, for example, that in all four tests (IA, IB, IIA, and IIB) the lighter smokers had a higher average control heart rate and a smaller average rise in heart rate on smoking, but that the average final heart rate was higher in two instances and lower in the other two.

TABLE VII. CONSISTENCY OF TRENDS OF MEAN VALUES IN THE FOUR GROUPS OF TESTS COMPARING THE LIGHTER AND HEAVIER SMOKERS (SERIES F)

MEASUREMENT	CONTROL		CHANGE		FINAL	
	LIGHTER SMOKERS	HEAVIER SMOKERS	LIGHTER SMOKERS	HEAVIER SMOKERS	LIGHTER SMOKERS	HEAVIER SMOKERS
Systolic pressure	4	0	1	3	3	1
Diastolic pressure	3	1	1	3	2	2
Pulse pressure	3	1	0	4	2	2
Heart rate	4	0	0	4	2	2
Stroke volume	1	3	3	1	1	3
Cardiac output	4	0	0	4	1	3

The numbers in Tables VII indicate in how many of the four groups of comparisons the mean value is the higher (in the direction of positivity) in the group concerned.

From the four such comparisons that can be made, it is possible to obtain only an over-all impression: that in the main the control values are higher more frequently in the lighter smokers, the change greater in the heavier smokers, and the final readings evenly distributed.

Effect of exercise habits: Since it is difficult to quantitate every-day exercise accurately, in studying its effect upon the response to smoking we have made a broad division as in the preceding section. Inquiry into the amount and kind of exercise during the preceding month was made at the time of each smoking test and the subjects classified as taking "no," "little," "moderate," or "much" exercise according to prearranged definitions. Two main groups were then formed by combining those taking no and little exercise on the one hand and moderate and much on the other. The resulting groups were of equal size. As before, the A and B tests were pooled with the same advantage from the reduction in size of the standard errors with little ill effect from slight loss of homogeneity of the material. The resulting groups are compared by mean values (Table VIII). The differences are not great: the less active subjects have a higher resting heart rate with a bigger rise on smoking and this is reflected in a greater rise and a higher final figure for the cardiac output. Other differences are not statistically significant.

It might be thought that the factors of smoking habits and exercise might influence each other: that the more athletic students are more sociable and more likely to smoke heavily; or conversely, that many of them are likely to be light smokers as a result of athletic training. In this way one would be comparing two groups, the composition of which differs in more than one respect. Accordingly, the association between these two factors has been analyzed (Table IX). It is clear that even if we look upon all the tests as having been performed on different individuals instead of four of them by each, the value for chi-square is not significant at the 5 per cent level, though it does seem that the less athletic subjects smoke more.

Volume 8
Number 2

TABLE VIII. THE

MEASUREMENT
Systolic pressure
Control
Change
Final
Diastolic pressure
Control
Change
Final
Pulse pressure
Control
Change
Final
Heart rate
Control
Change
Final
Stroke volume
Control
Change
Final
Cardiac output
Control
Change
Final

Where in the values are calcula
* P < 0.05.
** P < 0.01

TABLE IX.

EXERCISE HABITS	
Much	
Little	
Total	

The con
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reading (Tal

GROUPS OF TESTS COMPARING
ES F)

	FINAL	
R S	LIGHTER SMOKERS	HEAVIER SMOKERS
	3	1
	2	2
	2	2
	2	2
	1	3
	1	3

of comparisons the mean value

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"moderate," or "much"
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ı that the less athletic

TABLE VIII. THE EFFECTS OF EXERCISE HABITS ON THE RESULTS OF THE SMOKING TEST (SERIES F)

MEASUREMENT	LIGHT EXERCISE (L) MEAN	HEAVY EXERCISE (H) MEAN	L–H	t
Systolic pressure				
Control	113.48	114.83	−1.34	1.003
Change	4.06	5.28	−1.22	1.215
Final	117.55	120.11	−2.56	1.623
Diastolic pressure				
Control	65.58	68.02	−2.44	1.887
Change	4.64	5.55	−0.91	0.997
Final	70.22	73.56	−3.34	1.917
Pulse pressure				
Control	47.91	46.81	1.09	0.816
Change	− 0.58	− 0.27	−0.31	0.404
Final	47.33	46.55	0.78	0.542
Heart rate				
Control	63.42	60.36	3.06	2.038*
Change	13.47	10.12	3.34	1.940
Final	76.89	70.48	6.41	3.093**
Stroke volume				
Control	109.55	113.84	−4.29	1.502
Change	− 4.97	− 7.84	2.87	1.780
Final	104.58	106.00	−1.42	0.545
Cardiac output				
Control	6.89	6.82	0.07	0.358
Change	1.11	0.59	0.52	2.927**
Final	8.00	7.41	0.59	2.633*

Where in the above comparisons variance is significantly different in the two groups, probability values are calculated from weighted t values (Cochran's technique).

* $P < 0.05$.

** $P < 0.01$.

TABLE IX. CORRELATION BETWEEN THE EXERCISE AND SMOKING HABITS OF THE SUBJECTS

EXERCISE HABITS	SMOKING HABITS				TOTAL
	HEAVY SMOKERS		LIGHT SMOKERS		
	OBS.	EXP.	OBS.	EXP.	
Much	36	40	28	24	64
Little	44	40	20	24	64
Total	80		48		128

$\chi_1^2 = 1.633$ $p < 0.2$

The constancy of ceiling: One interesting fact that emerged from this analysis is that the final figure immediately after smoking was the most constant reading (Table IV, Fig. 1). These "ceiling" values varied so little that even if

TABLE X. VARIABILITY OF INDIVIDUAL RESPONSE TO SMOKING: MEAN VALUES AND STANDARD DEVIATIONS OF CIRCULATORY MEASUREMENTS IN EIGHT TESTS ON EACH OF SIX SUBJECTS (SERIES E)

SUBJECT NO.	VALUE	SYSTOLIC PRESSURE		DIASTOLIC PRESSURE		PULSE PRESSURE		HEART RATE		STROKE VOLUME		CARDIAC OUTPUT	
		MEAN	S.D.	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.
58127	Control	125.8	3.2	65.8	6.2	60.0	6.0	52.1	3.6	110.8	7.7	5.8	0.5
	Change	+12.5**	7.0	+12.2***	3.0	+ 0.2	6.9	+17.2***	5.3	− 4.3	12.2	+1.6**	1.0
	Final	138.3	7.9	78.0	4.4	60.2	6.3	69.3	2.8	106.5	8.6	7.4	0.7
58158	Control	110.9	3.6	65.6	3.0	45.2	4.7	69.8	7.7	99.7	8.9	6.9	0.7
	Change	+ 2.9	3.6	+ 7.0***	1.7	− 4.1*	4.8	+19.1***	4.9	− 9.5**	7.3	+1.1***	0.4
	Final	113.8	3.1	72.6	2.6	41.1	3.6	88.9	5.7	90.2	4.6	8.0	0.6
59170	Control	94.4	3.7	61.0	1.7	33.4	3.1	66.9	4.7	120.1	6.5	8.0	0.7
	Change	0.0	2.0	+ 0.8	2.4	− 0.8	1.7	+ 5.5**	4.4	+ 2.3	10.7	+0.8**	0.5
	Final	94.4	3.9	61.8	3.0	32.6	2.9	72.4	7.8	122.4	11.4	8.8	0.7
58102	Control	145.0	3.8	79.1	4.4	65.9	4.7	65.9	4.7	134.4	9.9	8.8	0.6
	Change	+ 3.5	5.9	+ 4.6	5.4	− 1.1	5.1	+10.4***	5.2	− 6.6*	8.5	+0.9**	0.5
	Final	148.5	4.9	83.7	3.7	64.8	2.9	76.3	6.3	127.8	7.7	9.7	0.4
59118	Control	112.1	5.9	70.8	8.1	41.4	4.6	61.1	7.5	124.5	6.7	7.6	0.8
	Change	+ 0.9	6.0	+ 1.0	2.7	− 1.9	4.0	+ 1.8	3.0	− 3.2	7.4	0.0	0.6
	Final	111.2	5.0	71.8	8.8	39.5	5.6	63.0	6.4	121.3	5.6	7.6	0.8
58152	Control	116.8	5.4	71.5	4.0	45.2	5.3	72.7	4.6	99.2	3.6	7.2	0.4
	Change	+ 0.9	2.5	+ 3.4	5.5	− 2.5	5.7	+ 1.2	5.5	+ 0.5	7.1	+0.2	0.4
	Final	117.6	4.3	74.9	5.1	42.7	3.8	73.9	5.6	99.7	5.1	7.4	0.5
Mean	Control	117.5	4.4	69.0	5.1	48.5	4.8	64.8	5.7	114.8	7.5	7.4	0.6
	Change	+ 3.1	4.9	+ 4.8	3.8	− 1.7	5.0	+ 9.2	4.8	− 3.5	8.1	+0.8	0.6
	Final	120.6	5.1	73.8	5.0	46.8	4.4	74.0	6.0	111.3	7.5	8.2	0.7

The probability estimates, showing that the change on smoking is significant, are made from "t" tests which compare the mean change on smoking with the variability of the mean change on smoking.

S.D. = standard deviation.

*P < 0.05.

**P < 0.01.

***P < 0.001.

Volume 8
Number 2

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Fig. 2.—The indi
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Table X and Fig. 3.

PERCENTAGE CHANGE AFTER ONE CIGARETTE

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subjects (*Series*
shows the averag
subjects on eight
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root mean varia
ject. The result
characteristics w
varying degrees
58152), were rep

Mean	Control	117.5	4.4	69.0	5.1	48.5	4.8	64.8	5.7	114.8	7.5	7.4	0.6
	Change	+3.1	4.9	+4.8	3.8	−1.7	5.0	+9.2	4.8	−3.5	8.1	+0.8	0.6
	Final	120.6	5.1	73.8	5.0	46.8	4.4	74.0	6.0	111.3	7.5	8.2	0.7

The probability estimates, showing that the change on smoking is significant, are made from "t" tests which compare the mean change on smoking with the variability of the mean change on smoking.
S.D. = standard deviation.
*P < 0.05.
**P < 0.01.
***P < 0.001.

the readings obtained under the most unlike circumstances are paired (i.e., those before breakfast on one day with those before lunch on the other) only two of the 36 combinations (5.6 per cent) are significantly different at the 5 per cent level—about the frequency one would expect by chance (Table V). This observation suggests that smoking a cigarette tends to push the various measurements to a ceiling, as if a cigarette at different times of day "takes up the slack" regardless of the control figure. Moreover, the ceiling was essentially the same for lighter and heavier smokers, and differences in habits of exercise did not affect it.

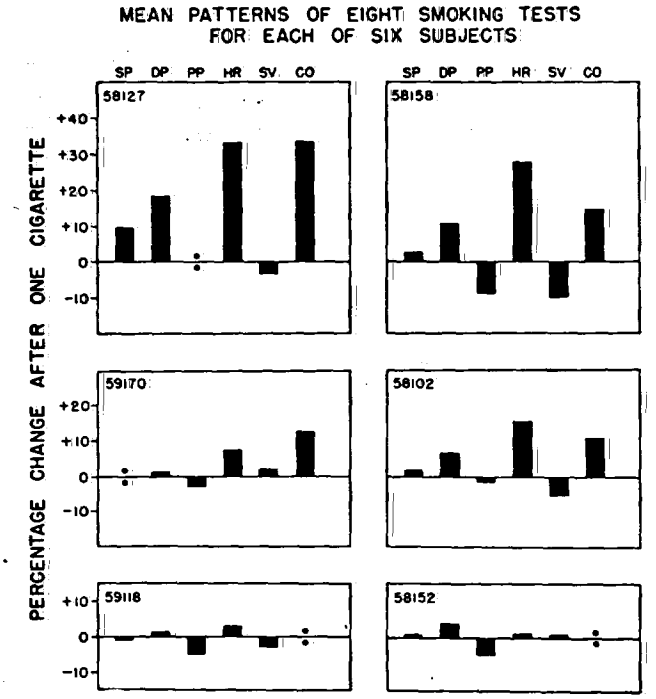

Fig. 2.—The individual circulatory response to smoking. Each column represents the mean of the changes in eight tests. The subjects are arranged in order of reactivity. The same order is used in Table X and Fig. 3.

The reproducibility and individuality of the measurements on repeated tests on subjects under standardized conditions: the series of eight tests on each of 6 subjects (*Series E*).—The results obtained are summarized in Table X which shows the average and standard deviation for each function measured in the six subjects on eight occasions. The bottom row shows the means of the 48 readings for each function with a mean of individual standard deviation (calculated as root mean variance). Fig. 2 shows the mean response to smoking of each subject. The results of repeated tests indicate that: (1) on the average, individual characteristics were maintained throughout the series of tests; (2) persons of varying degrees of reactivity, from marked (Subject 58127) to slight (Subject 58152), were represented among the test subjects. As might be expected, when

the subjects are arranged in order of decreasing responsiveness, most of the mean changes which are significantly greater than the standard deviations appear in the upper portion of the table (Table X).

From the average standard deviations, we have attempted to estimate the reliability of a single test on one subject, by taking twice this value as the 95 per cent confidence limits (Table XI). Thus the control reading for the systolic pressure, for example, in one test on a given subject will lie within 8.8 mm. Hg either way of the population mean for that person, provided that: (1) one such test is an unbiased estimate of the mean; and (2) differences between the variances of the several individuals are entirely explicable by chance and do not denote that some subjects are more variable in their response than others.

TABLE XI. CONFIDENCE LIMITS ON THE RESULTS OF A SINGLE TEST (SERIES E)

MEASUREMENT	MEAN STANDARD DEVIATION (ROOT MEAN VARIANCE)	MEAN MEAN	95% CONFIDENCE LIMITS (ABSOLUTE)
Systolic pressure			
Control	4.4	117.5	± 8.8
Change	4.9	+ 3.1	± 9.8
Final	5.1	120.6	±10.2
Diastolic pressure			
Control	5.1	69.0	±10.2
Change	3.8	+ 4.8	± 7.6
Final	5.0	73.8	±10.0
Pulse pressure			
Control	4.8	48.5	± 9.6
Change	5.0	− 1.7	±10.0
Final	4.4	46.8	± 8.8
Heart rate			
Control	5.7	64.8	±11.4
Change	4.8	+ 9.2	± 9.6
Final	6.0	74.0	±12.0
Stroke volume			
Control	7.5	114.9	±15.0
Change	9.1	− 3.6	±18.2
Final	7.5	111.3	±15.0
Cardiac output			
Control	0.6	7.4	± 1.2
Change	0.6	+ 0.8	± 1.2
Final	0.7	8.2	± 1.4

That the first premise is a valid assumption is seem in Table XII, where the results of the set of six first tests are averaged, then the second tests, the third, and so on. The averages of the first tests differ very little from the averages of the subsequent tests and are a very good estimate of the mean for all 48 tests. Similar results are obtained if the results are ranked. The second premise has been examined by Bartlett's test for homogeneity of variance, the results being presented in Table XIII. In 13 of the readings, differences appear to be no more than could be readily explained by chance. In the other five, including all three

TABLE XII. COMP

MEASUREMENT	FI
Systolic pressure	
Control	11
S.D.	1
Change	
S.D.	
Final	12
S.D.	1
Diastolic pressure	
Control	7
S.D.	
Change	
S.D.	
Final	
S.D.	
Pulse pressure	
Control	
S.D.	
Change	
S.D.	
Final	
S.D.	
Heart rate	
Control	
S.D.	
Change	
S.D.	
Final	
S.D.	
Stroke volume	
Control	
S.D.	
Change	
S.D.	
Final	
S.D.	
Cardiac output	
Control	
S.D.	
Change	
S.D.	
Final	
S.D.	

S.D. = Standard

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reading for the systolic
lie within 8.8 mm. Hg
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LE TEST (SERIES E)

	95% CONFIDENCE LIMITS (ABSOLUTE)
	± 8.8
	± 9.8
	±10.2
	±10.2
	± 7.6
	±10.0
	± 9.6
	±10.0
	± 8.8
	±11.4
	± 9.6
	±12.0
	±15.0
	±18.2
	±15.0
	± 1.2
	± 1.2
	± 1.4

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mean for all 48 tests.
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ive, including all three

TABLE XII. COMPARISON OF THE MEAN VALUES OF EIGHT SETS OF TESTS (SERIES E)

MEASUREMENT	FIRST	SECOND	THIRD	FOURTH	FIFTH	SIXTH	SEVENTH	EIGHTH	ALL
Systolic pressure									
Control	119.7	115.3	116.2	118.5	119.5	119.2	114.2	117.3	117.5
S.D.	18.1	14.3	15.1	18.6	17.0	16.7	19.6	19.0	16.2
Change	1.0	6.0	3.2	3.0	2.5	3.7	4.2	1.7	3.1
S.D.	4.0	2.3	5.7	8.5	9.4	9.7	7.5	2.7	6.5
Final	120.7	121.3	119.3	121.5	122.0	122.8	118.3	119.0	120.6
S.D.	17.8	15.5	20.5	22.8	20.6	22.9	21.0	19.4	18.7
Diastolic pressure									
Control	70.2	67.8	67.2	68.8	69.2	70.8	68.8	68.8	69.0
S.D.	8.8	6.3	7.7	7.1	6.5	7.3	11.8	7.4	7.5
Change	4.3	6.3	7.5	5.2	4.3	5.2	2.0	3.8	4.8
S.D.	6.2	5.8	4.5	6.7	5.3	5.4	5.6	3.2	5.3
Final	74.5	74.2	74.7	74.0	73.5	76.0	70.8	72.7	73.8
S.D.	8.4	5.3	10.5	7.3	7.6	8.3	12.5	8.9	8.3
Pulse pressure									
Control	49.5	47.5	49.0	49.7	50.3	48.3	45.3	48.5	48.5
S.D.	16.4	14.0	11.0	15.3	11.3	11.8	10.4	12.4	12.1
Change	−3.3	−0.3	−4.3	−2.2	−1.8	−1.5	2.2	−2.2	−1.7
S.D.	5.1	4.5	5.5	5.2	6.5	5.2	3.8	2.5	4.9
Final	46.2	47.2	44.7	47.5	48.5	46.8	47.5	46.3	46.8
S.D.	12.4	11.1	12.0	16.8	14.6	16.2	12.1	10.8	12.5
Heart rate									
Control	63.3	66.8	64.5	64.6	69.0	63.4	60.5	66.1	64.8
S.D.	10.4	6.1	9.1	8.3	11.9	8.8	10.3	5.1	8.6
Change	8.7	9.2	7.6	11.1	8.0	9.6	10.4	9.2	9.2
S.D.	8.5	8.8	12.0	6.1	7.5	10.8	9.4	7.8	8.4
Final	72.0	76.0	72.1	75.7	77.0	73.0	70.9	75.2	74.0
S.D.	14.4	9.5	11.6	9.5	9.6	8.0	10.8	7.7	9.8
Stroke volume									
Control	116.7	116.2	114.1	113.0	115.4	116.1	114.3	112.4	114.8
S.D.	17.1	15.8	19.3	15.7	22.6	13.3	8.2	11.2	14.8
Change	−0.5	−2.6	−2.5	−2.3	−4.4	−8.0	−5.8	−1.7	−3.5
S.D.	12.4	10.9	9.9	11.3	8.7	9.0	10.7	5.0	9.5
Final	116.2	113.6	111.6	110.6	111.0	108.1	108.4	110.7	111.3
S.D.	19.5	15.4	20.1	17.5	18.4	13.2	15.7	9.4	15.4
Cardiac output									
Control	7.34	7.77	7.32	7.27	7.60	7.35	6.90	7.42	7.40
S.D.	1.30	1.24	1.24	1.18	1.15	1.28	1.18	0.87	1.13
Change	0.83	0.83	0.57	0.99	0.64	0.54	0.73	0.90	0.75
S.D.	0.75	0.64	1.18	1.26	0.61	0.55	0.72	0.73	0.79
Final	8.18	8.60	7.90	8.26	8.44	7.89	7.63	8.32	8.15
S.D.	1.08	1.29	0.88	0.71	1.07	1.27	1.31	1.04	1.06

S.D. = Standard deviation.

diastolic readings, individual subjects seem to differ widely. Moreover, our main concern is with the change on smoking, and it transpires that the variability of the *change* of all three blood pressure readings, systolic, diastolic, and pulse pressure, differs significantly from individual to individual.

TABLE XIII. BARTLETT'S TEST FOR HOMOGENEITY OF VARIANCE IN THE DATA FROM SERIES E

MEASUREMENT	M′	p
Systolic pressure		
Control	4.206	0.75
Change	14.557*	0.025
Final	7.206	0.25
Diastolic pressure		
Control	16.885**	0.005
Change	13.99*	0.025
Final	14.107*	0.025
Pulse pressure		
Control	2.857	0.75
Change	11.263*	0.05
Final	7.524	0.25
Heart rate		
Control	6.072	0.5
Change	2.777	0.75
Final	6.211	0.5
Stroke volume		
Control	6.821	0.25
Change	3.958	0.75
Final	8.227	0.25
Cardiac output		
Control	3.499	0.75
Change	8.399	0.25
Final	3.912	0.75

M′ = Bartlett's index for homogeneity of variance (M), corrected for small sample size. A significant value for M′ indicates that variance differs from one subject to another. It is read as a χ^2 value (degrees of freedom: $6-1=5$).

* $P < 0.05$. ** $P < 0.01$.

It seems then that our confidence limits may be applied to the first smoking test, and, in an individual test, probably to the heart rate, stroke volume, and cardiac output, but not to the blood pressure values. In other words, not only the mean, but also the variance is an individual characteristic: for some subjects, our confidence limits are too broad, and for others, too narrow. We have no way of predicting which of these errors is likely in any particular subject; regressions of variance on the mean show no significant correlation. In the main, of course, we will be able to distinguish "hypo-" from "hyper-" reactors, but from time to time we may make errors, and it is perhaps best to apply our confidence limits, especially for the blood pressure responses, to groups only. A standard error is easily computed from our confidence limits.

The object of the smoking test is to characterize a given subject according to the degree and direction of change in regard to each variable, and the success

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on repeated tes
test is reliable
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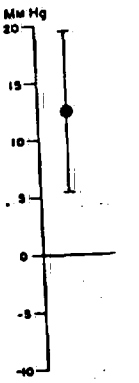

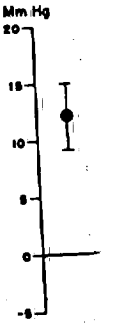

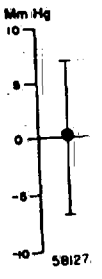

Fig. 3.—Int
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HE DATA FROM SERIES E

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of the test depends on the contrast between individual variation (intraindividual) on repeated tests and variation between individuals (interindividual). A single test is reliable if the intraindividual scatter is relatively small compared with the interindividual variation, but if there is not much difference between the intra- and interindividual variation, then the test will be of little value as a screening procedure. This question is best answered by an analysis of variance (Fig. 3).

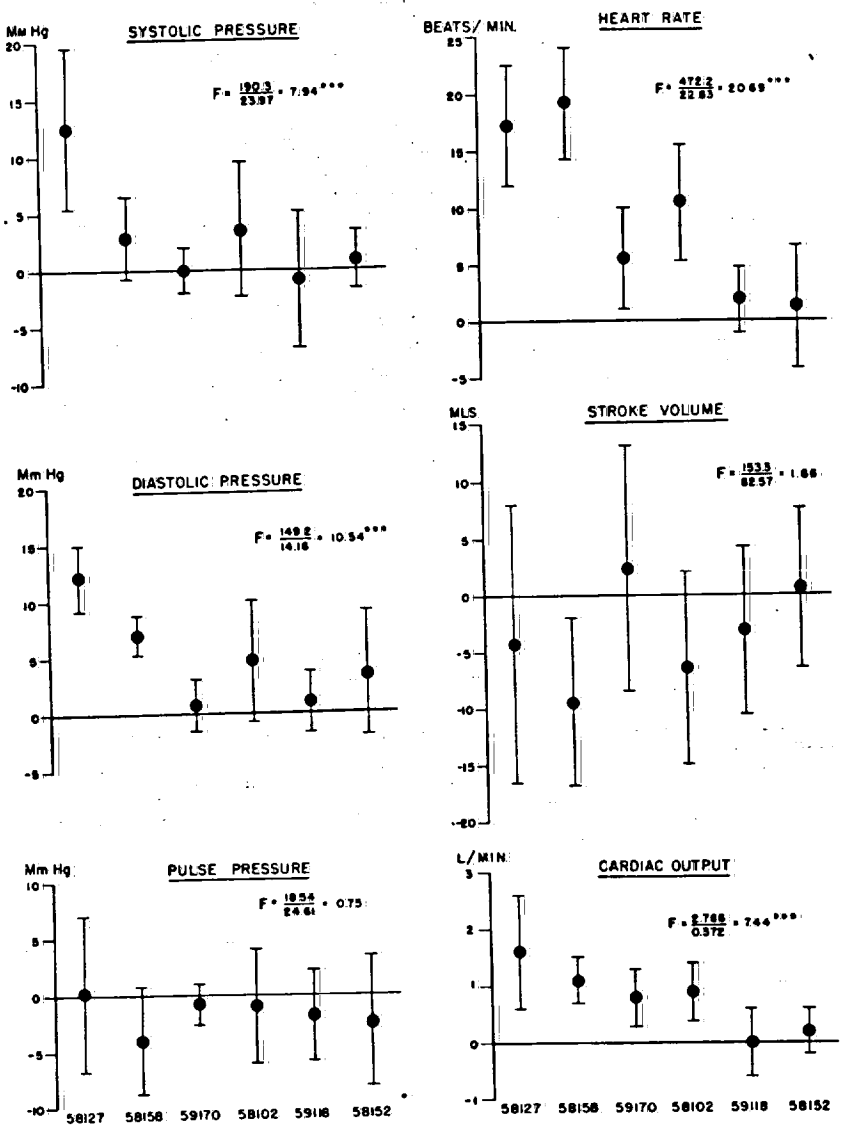

Fig. 3.—Intraindividual variation in eight smoking tests on each of 6 subjects. In each instance, the black circle marks the mean value and the lines one standard deviation above and below it. F represents the ratio of interindividual to intraindividual variance and is an indication of the confidence with which subjects may be classified according to the magnitude of the response. ***P <0.001.

Since we are chiefly concerned with *change* on smoking, the data concerning individuality of resting values, which is a matter of common experience, will not be presented here.

The variance obtained by pooling all 48 sets of readings of the change in systolic pressure after smoking, for example, arises from two sources: intraindividual variation as shown in Table X and interindividual variation which is found by subtracting the intraindividual variation from the total variation. We can then set up an analysis of variance as follows:

Source of variation	*Degrees of freedom*	*Sum of squares*	*Mean square*
Interindividual	$6-1=5$	951	190.3
Intraindividual	$6\,(8-1)=42$	1007	23.97
Total	$(6\times 8)-1=47$	1958	—

The ratio of the two mean squares (interindividual variation being always the numerator) is designated "F" and corresponding values for p are obtained from appropriate tables with (5,42) degrees of freedom. The value for F in this example is 7.94 which gives $p < 0.001$. From analyses similar to this we find that changes in systolic and diastolic pressure, heart rate, and cardiac output are fairly individual, and are likely to produce a satisfactory subdivision of our subjects, whereas changes in pulse pressure and stroke volume are not, except perhaps in rare instances. These findings agree with our previous general impressions.

TABLE XIV. COMPARISON OF VARIANCE IN THE CONTROL AND FINAL FIGURES IN SERIES E

SUBJECT NO.	VALUE	SYSTOLIC PRESSURE	DIASTOLIC PRESSURE	PULSE PRESSURE	HEART RATE	STROKE VOLUME	CARDIAC OUTPUT
58127	Control	10.00	38.86	36.57	13.33	58.60	0.284
	Final	62.29	19.71	40.29	7.95	74.74	0.519
	r	−0.77*	+0.61	−0.05	+0.27	−0.12	−0.30
58158	Control	13.29	9.12	21.93	59.30	80.04	0.454
	Final	9.36	6.86	12.70	31.98	21.03	0.398
	r	+0.19	+0.25	+0.28	+0.44	+0.66	+0.10
59170	Control	13.43	2.86	9.71	22.14	41.89	0.490
	Final	15.14	8.86	8.57	51.52	128.86	0.507
	r	−0.12	−0.59	+0.12	−0.73*	−0.54	−0.03
58102	Control	14.57	19.27	22.13	21.74	98.12	0.353
	Final	24.00	13.36	8.50	39.06	58.64	0.176
	r	−0.25	+0.18	+0.45	−0.34	+0.30	+0.38
59118	Control	34.70	65.64	21.13	55.81	44.68	0.628
	Final	25.36	77.93	31.71	41.43	30.88	0.714
	r	+0.17	−0.27	−0.28	+0.35	+0.19	−0.11
58152	Control	28.79	16.00	28.64	21.13	12.83	0.160
	Final	18.27	26.14	14.21	31.29	26.21	0.267
	r	+0.44	−0.25	+0.33	−0.21	−0.36	−0.31

*$P < 0.05$. r = correlation coefficient.

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AL FIGURES IN SERIES E

STROKE VOLUME	CARDIAC OUTPUT
58.60	0.284
74.74	0.519
−0.12	−0.30
80.04	0.454
21.03	0.398
+0.66	+0.10
41.89	0.490
128.86	0.507
−0.54	−0.03
98.12	0.353
58.64	0.176
+0.30	+0.38
44.68	0.628
30.88	0.714
+0.19	−0.11
12.83	0.160
26.21	0.267
−0.36	−0.31

It is of some interest to compare the variability of the control and the final readings in Series E. The variances for each kind of measurement are set forth in Table XIV. The most sensitive way of detecting differences between these two readings is by Pitman's technique, which is designed for comparing the variances of paired measurements.[3] Only two of the 36 correlation coefficients so obtained are significant at the 5 per cent level, and since this is about what would be expected to occur by chance, there is no evidence that final readings in Series E are any less variable than the control readings. This marked contrast to what was found in Series F remains to be explained but may will lie in the different test conditions of Series E and Series F: in Series E, all eight control readings were made at a single time of day, whereas in Series F, two control readings were obtained before breakfast and two before lunch under somewhat different conditions.

Comparison between the Results Obtained in the Different Series of Smoking Tests.—We have thus far considered the reproducibility of the results under rigorously standardized conditions and also some of the factors which seem to influence the size of the response. It now remains to compare the results obtained with the different degrees of standardization of the test conditions to seen if in fact these materially affect the results.

In Table XV the variances in Series O and Series F are compared. In each instance the variance in the former is divided by that in the latter, the significance of the F value so obtained being read from two-tailed tables. If the values are significantly greater than one then the variance is significantly greater in the O Series while if significantly less than one the converse is true. It is apparent that of the 72 values obtained, 19 are significantly different from one, 8 of them at the 1 per cent level. Notwithstanding these marked differences, there is no readily recognizable pattern in the results: in 10 instances, the variance is significantly greater than one (6 at the 5 per cent level and 4 at the 1 per cent level of probability) and in 9 significantly less than one (5 at the 5 per cent level and 4 at the 1 per cent level). There appears to be a definite trend: most of the 5 per cent and all of the 1 per cent probabilities in which the Series O reading is greater are seen to occur in the blood pressure readings, and the converse appears for the heart rate, stroke volume, and cardiac output. These comparisons of variance are of more importance in comparing the mean values, since in the appropriate cases it is necessary to calculate "t" values by Cochran's technique, for comparing two groups of unequal numbers and significantly different variances. In Table XVI we have computed the algebraic differences between the means of the 69 single tests on the one hand and those of the four sets of tests in Series F on the other. The significance of these differences is indicated in the usual way. There is no very striking pattern, but it does appear that where there is a significant difference, in most instances, the control readings are higher in Series O, the change on smoking higher in Series F, and the final readings about evenly distributed.

Series O is compared with the eight tests in Series E in Tables XVII and XVIII. The former compares the variances by the same method as in Table XV. Twenty-one of the 144 results are significantly different from unity: 14

TABLE XV. COMPARISON OF THE VARIANCE IN SERIES O AND F

MEASUREMENT	VARIANCE RATIOS O/IA	O/IIA	O/IB	O/IIB
Systolic pressure				
Control	2.44**	1.30	1.65	1.18
Change	0.855	0.870	3.70**	1.33
Final	1.35	0.926	2.32*	1.01
Diastolic pressure				
Control	0.735	0.833	0.855	1.23
Change	0.800	0.763	1.37	0.952
Final	0.549*	0.485*	0.714	0.658
Pulse pressure				
Control	1.44	1.62	1.91*	1.34
Change	2.19*	2.47**	3.68**	2.23*
Final	1.87	1.88	1.51	1.11
Heart rate				
Control	1.60	1.88	2.03*	1.81
Change	0.452**	0.330**	0.654	1.21
Final	1.08	0.671	1.29	0.935
Stroke volume				
Control	1.01	1.08	0.990	1.09
Change	0.451**	0.490*	0.526*	0.730
Final	1.44	2.09*	1.40	1.33
Cardiac output				
Control	1.88	1.64	1.31	1.44
Change	0.543*	0.351**	0.714	0.847
Final	1.60	1.10	1.50	1.20

*P < 0.05. **P < 0.01.

of these (6 at the 5 per cent level and all 8 at the 1 per cent level) occurred in the systolic pressure readings, only 5 occurring in the remaining 120 values and all at the 5 per cent level. In almost all instances these values are significantly less than unity, a reflection of the fact that the groups of subjects being compared are of such unequal sizes (69 and 6, respectively) which means that the variance in group O has to be relatively very much larger to reach a significant level. Thus if we examine all readings other than systolic pressure, we find that 64 values are less than unity and 56 more. Again, however, in the systolic readings, only 4 of the 24 values are greater than unity. It seems, then, as if the only real difference in the two groups is that the systolic pressure is almost uniformly more variable between individuals in conditions standardized for each individual separately (but not uniform from one individual to another) than that within a large group of individuals under random conditions. The significance of this is obscure unless it be that there was a different observer in Series E (E.A.M.) or the fact that the latter subjects were in part selected. As before, we are mainly interested in using variance to assess the significance of differences in the mean values. It is clear from Table XVII that these are unimpressive.

TABLE XVI.

MEASUREMENT
Control
Systolic pressure
Diastolic pressure
Pulse pressure
Heart rate
Stroke volume
Cardiac output
Change
Systolic pressure
Diastolic pressure
Pulse pressure
Heart rate
Stroke volume
Cardiac output
Final
Systolic pressure
Diastolic pressure
Pulse pressure
Heart rate
Stroke volume
Cardiac output

* P < 0.05.
** P < 0.01.
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TABLE XVI. COMPARISON BETWEEN THE MEAN VALUES IN SERIES O AND F

MEASUREMENT	O–IA	O–IIA	O–IB	O–IIB	SIGNIFICANT DIFFERENCES	
					POSITIVE	NEGATIVE
Control						
Systolic pressure	1.0	1.3	−0.8	−1.3	0	0
Diastolic pressure	7.9***	4.6**	4.6**	4.7***	4	0
Pulse pressure	−4.3*	−3.3	−5.4**	−6.0***	0	3
Heart rate	10.0***	10.8***	7.7***	6.8**	4	0
Stroke volume	0.3	−0.9	−1.3	−10.5**	0	1
Cardiac output	1.12***	1.09***	0.73**	0.38	3	0
Change						
Systolic pressure	−2.8*	−3.9**	0.2	−1.7	0	2
Diastolic pressure	−0.2	−1.0	1.2	−1.1	0	0
Pulse pressure	−2.6*	−3.0**	−1.3	−0.7	0	2
Heart rate	−5.8**	−5.8*	−4.2*	−1.8	0	3
Stroke volume	2.4	1.7	2.7	3.2	0	0
Cardiac output	−0.56*	−0.63*	−0.31	−0.08	0	2
Final						
Systolic pressure	−1.8	−2.6	−0.6	−3.0	0	0
Diastolic pressure	5.1*	3.6	6.0**	3.6	2	0
Pulse pressure	−6.9***	−6.3**	−6.7***	−6.7**	0	4
Heart rate	4.2	5.0	3.5	5.0	0	0
Stroke volume	2.7	0.8	1.4	−2.3	0	0
Cardiac output	0.56*	0.46	0.42	0.30	1	0

* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

These comparisons show that we have gained little by attempting to standardize the conditions of the test beyond those laid down for the original studies, of which Series O was a part.[1] The presence or absence of the fasting state appears to be the only factor of general importance.

Discussion: While many of the inferences to be drawn from the facts presented in the foregoing section have been mentioned, certain points deserve emphasis. In both Series F and Series E, we have found that the circulatory changes on smoking as measured in the first test are an unbiased estimate of the mean: although the mean of the results in repeated tests would give more information than a single test, nevertheless the first test is as accurate and informative as any other single test. This conclusion fulfills a most important requirement for a test which is to be useful as a screening procedure. Moreover, an analysis of variance showed that the intraindividual variations of systolic pressure, diastolic pressure, heart rate, and cardiac output are significantly smaller than the interindividual variations. This separation is an even more important requisite for a screening test, because it makes it possible with fair confidence to assign subjects to one of several broad groups according to the magnitude and direction of the response. These findings support the view previously formed that individual differences in the patterns of circulatory change on smoking have

TABLE XVII. COMPARISON OF THE VARIANCE IN SERIES O AND E

MEASUREMENT	FIRST	SECOND	THIRD	FOURTH	FIFTH	SIXTH	SEVENTH	EIGHTH
Systolic pressure								
Control	0.284*	0.452	0.408	0.267**	0.321*	0.332*	0.241**	0.258*
Change	2.28	7.02*	1.13	0.500	0.417	0.385	0.649	4.89
Final	0.316	0.422	0.239**	0.194**	0.250**	0.192**	0.228**	0.267**
Diastolic pressure								
Control	0.629	1.22	0.826	0.962	1.16	0.917	0.336*	0.893
Change	0.625	0.730	1.04	0.543	0.870	0.893	0.763	2.38
Final	0.840	2.10	0.538	1.11	1.07	0.862	0.380	0.752
Pulse pressure								
Control	0.323*	0.448	0.719	0.373	0.690	0.625	0.906	0.571
Change	1.74	2.27	1.47	1.67	1.07	1.66	3.18	7.31*
Final	0.671	0.840	0.719	0.362	0.481	0.392	0.704	0.877
Heart rate								
Control	1.14	3.33	1.74	1.78	0.877	1.60	1.16	4.77
Change	0.667	0.617	0.334*	1.28	0.625	0.415	0.543	0.794
Final	0.633	1.44	0.971	1.45	1.42	2.03	1.11	2.19
Stroke volume								
Control	0.855	1.00	0.676	1.02	0.490	0.662	3.74	2.00
Change	0.283*	0.369	0.444	0.342*	0.578	0.549	0.383	1.77
Final	0.704	1.25	0.735	0.971	0.885	1.71	1.20	3.38
Cardiac output								
Control	0.943	1.04	0.909	1.14	1.20	0.971	1.00	2.10
Change	1.01	1.34	0.405	0.360*	1.52	1.82	1.72	1.06
Final	1.79	1.25	2.71	4.18	1.80	1.29	1.10	1.93

These figures were obtained by dividing the variance in Series O by those in Series E.
*P < 0.05.
**P < 0.01.

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MEASUREMENT
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TABLE XVIII. COMPARISON OF THE MEANS IN SERIES O AND E

MEASUREMENT	FIRST	SECOND	THIRD	FOURTH	FIFTH	SIXTH	SEVENTH	EIGHTH
Systolic pressure								
Control	5.5	1.1	2.0	4.3	5.3	5.0	0.0	3.1
t	0.74	0.18	0.32	0.56	0.75	0.72	0.0	0.40
Rise	−1.6	3.4	0.6	0.4	−0.1	1.1	1.6	−0.9
t	0.89	2.79*	0.25	0.11	0.03	0.27	0.51	0.68
Final	3.9	4.5	2.5	4.7	5.2	6.0	1.5	2.2
t	0.53	0.70	0.30	0.50	0.63	0.64	0.17	0.27
Diastolic pressure								
Control	−1.4	−3.8	−4.4	−2.8	−2.4	−0.8	−2.8	−2.8
t	0.38	1.40	1.35	0.92	0.86	0.26	0.57	0.89
Rise	−0.6	1.4	2.6	0.3	−0.6	0.3	−2.9	−1.0
t	0.23	0.58	1.27	0.11	0.27	0.13	0.39	0.70
Final	−2.0	−2.3	−1.8	−2.5	−3.0	−0.5	−5.6	−3.8
t	0.56	0.97	0.41	0.80	0.94	0.14	1.08	1.01
Pulse pressure								
Control	6.9	4.9	6.4	7.1	7.7	5.7	2.7	5.9
t	1.01	0.84	1.38	1.12	1.62	1.15	0.61	1.14
Rise	−1.0	2.0	−2.0	0.1	0.4	0.8	4.5	0.1
t	0.48	1.01	0.83	0.04	0.14	0.35	2.60*	0.08
Final	5.9	6.9	4.4	7.2	8.2	6.6	7.2	6.0
t	1.13	1.47	0.87	1.03	1.35	0.98	1.42	1.31
Heart rate								
Control	−7.5	−3.9	−6.3	−6.2	−1.8	−7.4	−10.3	−4.7
t	1.69	1.38	1.71	1.70	0.36	1.94	2.34	1.89
Rise	1.2	1.7	0.1	3.6	0.5	2.1	2.9	1.7
t	0.34	0.46	0.02	1.36	0.14	0.47	0.74	0.52
Final	−6.3	−3.2	−6.2	−3.4	−1.3	−5.3	−7.4	−3.1
t	1.06	0.77	1.26	0.83	0.31	1.49	1.60	0.90
Stroke volume								
Control	7.0	6.5	4.4	3.1	5.7	6.4	4.7	2.7
t	0.97	0.97	0.52	0.47	0.61	0.79	1.22	0.55
Rise	3.3	1.2	1.3	1.5	−0.6	−4.2	−2.0	2.1
t	0.64	0.26	0.33	0.32	0.16	1.12	0.45	0.96
Final	10.3	7.7	5.7	4.7	5.1	2.2	2.5	4.8
t	1.19	1.16	0.67	0.63	0.66	0.38	0.37	1.10
Cardiac output								
Control	−0.35	−0.80	−0.37	−0.42	−0.09	−0.35	−0.79	−1.27
t	0.64	1.52	0.75	0.83	0.02	0.64	1.47	3.29*
Rise	0.36	0.36	0.10	0.52	0.17	0.07	0.26	0.43
t	1.14	1.29	0.20	1.01	0.65	0.29	1.04	1.39
Final	0.02	0.44	−0.26	0.10	0.28	−0.27	−0.53	0.16
t	0.04	0.79	0.65	0.30	0.59	0.49	0.90	0.35

In each instance the O value was subtracted from the E value.
*P < 0.05.

Cardiac output								
Control	0.943	1.04	0.909	1.14	1.20	0.971	1.00	2.10
Change	1.01	1.34	0.405	0.360*	1.52	1.82	1.72	1.06
Final	1.79	1.25	2.71	4.18	1.80	1.29	1.10	1.93

These figures were obtained by dividing the variance in Series O by those in Series E.
*P < 0.05.
**P < 0.01.

real meaning and are not artefacts due to variance. It is worth noting, however, that the scatter of the results within the individual varies appreciably from subject to subject, so that confidence limits may be safely applied to groups only.

On repeated tests, the changes after smoking which characterized the 6 subjects in Series E were, in descending order of effectiveness, heart rate, diastolic pressure, systolic pressure, and cardiac output. Changes in pulse pressure and stroke volume did not provide good separation for these 6, but might do so for

larger and more representative groups. It was previously shown that there was quite good correlation between the pattern of response to smoking and the family history regarding hypertension or coronary disease.[1] As a group, subjects with parental hypertension showed a significantly greater rise in cardiac output than expected, while stroke volume and cardiac output were significantly smaller than expected among the offspring of parents with coronary disease. Changes in blood pressure and heart rate were not significantly different for these two small groups of subjects compared with those with normal parents, but levels of significance were approached in several instances. Accordingly, at present, cardiac output alone has been shown to have *both* important properties—that of giving satisfactory separation of subjects and of giving good correlation with family history. While the family history provides only indirect evidence of liability to future cardiovascular disease, it appears that, taken in conjunction with certain individual characteristics, it is helpful in pointing out susceptible persons.[4-6] From the above facts it appears that change in cardiac output after smoking is likely to be the most valuable part of the ballistocardiographic smoking test in screening possible candidates for hypertension or coronary disease.

In this paper, we have attempted to discover whether there are any factors which influence the response to smoking, since elimination of such sources of variation might "sharpen" the results. The only factor which seems important is the presence or absence of the fasting state which appears to change the magnitude of the response. This raises the question as to whether the tests performed before breakfast are measuring the same tendencies as those performed before lunch, that is, will the subjects tested before breakfast show a proportionate change if tested before lunch? In order to answer this question, we have calculated correlation coefficients between the results of the four sets of tests. Table XIX indicates that heart rate and cardiac output show good agreement.

TABLE XIX. CORRELATION COEFFICIENTS BETWEEN THE RESPONSES TO SMOKING (SERIES F)

MEASUREMENT	IA AND IB	IIA AND IIB	IA AND IIA	IB AND IIB
Systolic pressure	+0.202	+0.669***	+0.267	+0.500**
Diastolic pressure	+0.144	+0.641***	+0.242	+0.443*
Pulse pressure	−0.211	+0.225	−0.174	+0.178
Heart rate	+0.670***	+0.726***	+0.776***	+0.497**
Stroke volume	+0.158	−0.005	+0.050	+0.296
Cardiac output	+0.596***	+0.660***	+0.582***	+0.525**

* P < 0.05.
** P < 0.01.
*** P < 0.001.

This agreement is equally good whichever way the results are paired. Systolic and diastolic pressures show less satisfactory agreement. It seems legitimate then to conclude that the tests before breakfast and before lunch give similar information, but since the changes are on the average greater before breakfast, there is less danger that they will be obscured by experimental error. However, as shown in Table II, this increase in sensitivity has little practical effect on the

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o Smoking (Series F)

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	+0.443*
**	+0.178
	+0.497**
-*	+0.296
	+0.525**

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significance of the change after smoking, and there is little further difference between those done before lunch and those done at random (Table XVI). Accordingly, from our studies we conclude that there is little to be gained from fasting tests, and that tests performed at random times of day are satisfactory.

We have found few papers that deal with the quantitative aspects of the effect of smoking on the normal ballistocardiogram, and none which reported on the reproducibility of results.[7-9] Indeed, a search of the literature has shown that there is very little information on the reproducibility of the results obtained in repeated smoking tests of any type on the individual. The only reference which we have encountered is in a paper by Roth, in 1956, who writes, ". . . the increase in blood pressure and pulse rate during smoking varied little from day to day."[10] Unfortunately, she provides no figures or analysis of her results. In an earlier paper, however, the changes in blood pressure and heart rate after smoking are recorded for nine tests on one normal subject.[11] Calculation of standard deviations in this one case gave excellent agreement with the mean standard deviations in our Table X.

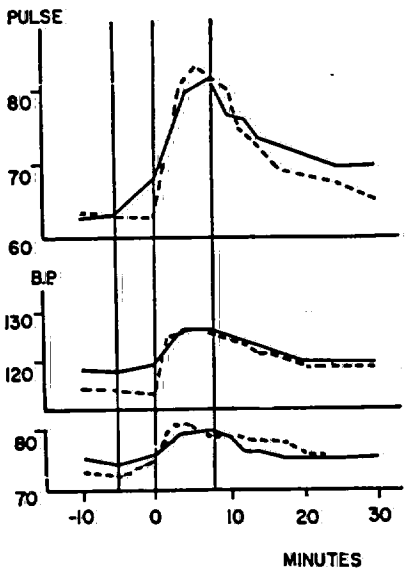

Fig. 4.—The influence of the fasting state on the circulatory response to smoking: average changes in 10 healthy subjects. From above down: pulse rate in beats per minute, systolic and diastolic pressure in mm. Hg. The broken line indicates the average of smoking tests performed in the fasting state, the solid line shows the average of tests in which a meal of pea soup immediately preceded smoking. The three vertical lines denote the times of beginning the meal (−5 minutes) starting to smoke (0 minutes) and finishing smoking (7½ minutes). It will be seen that in all measurements the value at 0 min. was lower when the subjects were fasting, but they showed a bigger rise on smoking and the "final" fasting figures (at 7½ minutes) were almost identical with the nonfasting values. (Modified from Ruosteenoja, R.: Effect of Food Intake on the Cardiovascular Response to Cigarette Smoking, Ann. Med. Exper. Fenn. **33**:320, 1955.)

Ruosteenoja compared the circulatory changes in 10 students aged 20 to 25 years (5 regular and 5 occasional smokers) under three sets of circumstances: immediately after a meal, on smoking after a meal, and on smoking after 15

hours' fasting.[12] In all other respects the test conditions were kept constant. These experiments show that there was a greater rise in skin temperature, systolic and diastolic pressure, and in pulse rate if the subject was fasting than there was after a meal (Fig. 4). In contrast to changes in skin temperature, which were highly significant, the differences in blood pressure and pulse rate were just significant at the 5 per cent level of probability. Although he makes no comment on the point, it appears from his diagrams, that the control values immediately before smoking were lower in the fasting state, and the highest figures after smoking were about the same whether or not the subjects were fasting. These data, therefore, agree nicely with our concept of the ceiling phenomenon which we have postulated as a result of the findings in Series F.

In a somewhat older group, Roth and Sheard found smaller differences in blood pressure and heart rate than we did when the changes on smoking in the fasting and nonfasting states were compared.[13] The discrepancies between their results and ours, however, do not seem great and may well result from differences in age and other characteristics of the subjects studied, as well as in the timing of the observations in relation to the last meal.

SUMMARY

1. A total of 245 ballistocardiographic smoking tests were done on healthy male medical students, all of them smokers. Sixty-nine subjects (Series O) had one test each at a random time in the day. To test the reproducibility of results 32 men had four tests each, two before breakfast and two before lunch (Series F) and 6 subjects had eight tests each under circumstances kept as standard as possible in every way (Series E).

2. The findings on a single smoking test in 113 students previously described, were essentially unchanged when the nonsmokers and female students were excluded, leaving the 69 subjects of Series O.

3. In 32 male smokers (Series F), smoking a cigarette before lunch produced results similar to those in Series O: a highly significant mean rise in systolic and diastolic pressure, heart rate, and cardiac output, and a fall in stroke volume. Pulse pressure was little affected. Compared with these tests, those performed before breakfast showed lower control readings, with a complementary increase in the response to smoking, so that the final figures after smoking were remarkably constant. Results were essentially the same on a second day. Heavier smokers tended to have lower control values and a bigger response to smoking. Exercise habits influenced the results little.

4. In the eight tests repeated on each of 6 subjects, the first test appeared to be an unbiased estimate of the mean. The reproducibility of the results was calculated, and it proved to be an individual characteristic, that is, mean confidence limits are of value in groups of subjects only. Analysis of variance shows that the change in systolic and diastolic pressures, heart rate, and cardiac output after smoking are likely to prove of value in classifying the subjects, but that for the other two measurements, the "overlap" of individual variation appears to be too great.

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5. Comparison of the three series of tests revealed no great differences. The results in Series O, Series E, and the tests before lunch in Series F were substantially the same. The findings in Series F before breakfast were the only exceptions: in the main, control readings were lower and the response to smoking proportionately greater at that time than in any other series of tests. However, this enhancement of response seems of little practical value.

6. From these findings it appears that the ballistocardiographic smoking test, in which blood pressure, heart rate, stroke volume, and cardiac output are measured, gives results which are sufficiently reproducible for use as a screening test to classify young adults according to their patterns of circulatory reactivity. The results were materially unchanged by attempts to standardize further the test conditions, except that on the average, the response was more marked in the fasting state.

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